Linearity of the BOLD response to varying durations of stimulus "OFF" periods

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Purpose:
To characterize the linearity of the blood oxygenation level dependent (BOLD) response to different durations of stimulus "OFF" periods.

Introduction:
Recent studies of the blood oxygenation level dependent (BOLD) fMRI signal in response to stimuli of different durations have revealed that the signal behaves in a nonlinear manner, with short duration stimuli producing responses larger than expected from a linear system. This nonlinearity is believed to result either from an overshoot in the neuron activity in response to the stimulus onset, or from nonlinearities within the hemodynamics, such as slower blood volume changes or the nonlinear dependence of oxygen extraction on flow, which translate the neuronal activity to the BOLD signal (1). No studies have yet characterized the linearity of the response to stimulus "OFF" periods. A study of these dynamics has the potential to lend insight into the origin of the hemodynamic response characteristics, since signal decreases in response to the cessation of a stimulus involve different dynamics in the relationship of blood flow, blood volume, and oxygen extraction, and perhaps neuronal activity. Blood flow is at a higher level, and thus changes in flow operate on a different part of the oxygen extraction vs. flow curve. A transient decrease in flow can therefore cause different BOLD signal changes than a transient increase from the resting state. Additionally, the blood volume is elevated and decreases with a slower time constant than blood flow changes (2), thus having a different effect depending on the duration of the OFF period.

Methods:
Multiple series of 310 axial T2*-weighted echo-planar images were acquired on a 3T GE Signa magnet (TR:1000ms, TE:30ms, FOV:24cm, slice thickness:5mm). A visual stimulus consisting of a contrast-reversing checkerboard was presented during this acquisition, with brief stimulus "OFF" periods (fixation onto a dark screen) presented every 20 seconds for durations of 2, 3, 4, 8, or 16 seconds. The stimulus was also presented in a blocked design, alternating 30 s of rest with 30 s of stimulation. The activated region was defined by correlating the response to the blocked design with an ideal response.
The Linearity was assessed by shifting and adding the average response to shorter duration OFF periods to predict the response to longer duration stimuli. The measured response was also compared to an ideal linear response (scaled to match the response to the longest duration stimulus). Finally, simulations with the balloon model were performed to see if this model predicts any nonlinearities and agrees with the observations.

Results:
The BOLD response behaved approximately linear for stimulus OFF periods greater than 4 seconds, but nonlinearly at shorter OFF periods, with signal decreases *less* than expected from a linear model (see Fig. 1). The response to shorter duration OFF periods consistently underestimated the response to longer duration stimuli. In some brain regions, an increase in the BOLD signal was observed in response to cessation of the stimulus. The duration of this positive response was independent of the stimulus "OFF" period.

Discussion:
There are several possibilities for the observed nonlinearity. First, the voxel could contain a sub-population of neurons that activate upon cessation of the stimulus, producing a continuing increase in blood flow, and a higher BOLD signal (a smaller decrease) than expected. Alternatively, the nonlinear relationship between blood flow and the BOLD signal may produce a smaller BOLD signal change for a given flow change. Simulations with the balloon model (3) suggest that this is sufficient to account for the observed nonlinearities. Simultaneous measurements of blood flow and BOLD signal changes will help to further characterize this nonlinearity.

Conclusion:
The BOLD response is nonlinear at short durations of stimulus OFF periods, with signal decreases smaller than expected.

References:
1. A. Vazquez et al., *NeuroImage* 7, 108-118, 1998
2. JB Mandeville et al., *JCBFM* 19(6):679-89, 1999.
3. RB Buxton et al., *Magn. Res. Med.* 39, 855-864, 1998.

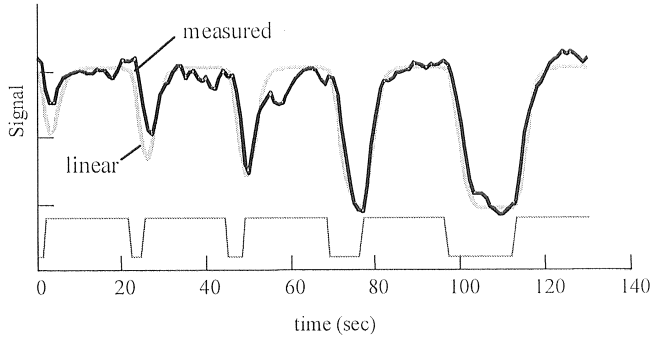

Figure 1: Measured BOLD response (dark line) and ideal linear prediction (gray line) for visual stimulation with "OFF" periods of 2, 3, 4, 8, and 16 s. For short "OFF" durations, the BOLD decrease is smaller than predicted.